REMARKS

The Examiner's reconsideration of the application is requested in view of the new claims set above and comments which follow.

So that the record will be clear, claims 49, 52 and 55 are new claims. Claims 50 corresponds to previous claim 34, as amended and claim 51 corresponds to previous claim 27. Claim 53 corresponds to previous claim 35 as amended and claim 54 corresponds to claim 36. Finally, claim 56 corresponds to previous claims 38 as amended, and claim 57 corresponds to claim 39 as amended.

Rejection under 35 U.S.C. 112, second paragraph (item 5-6)

The term "by binding to a site of the said factor or complex" no longer appears in the claims as filed herewith, thus rendering this objection moot.

Without acquiescence of the Examiner's objections, the term "by on purpose immunization in animals" has been omitted from claim 51 (corresponding to former claim 33).

The reference to "monoclonal antibodies" in claims 56 and 57 (corresponding to previous claims 38 and 39) has been changed to the singular form as suggested by the Examiner.

Rejection under 35 U.S.C. 101 (item 7)

The term "purified" has been added to claims 50 to 52 (corresponding to previous claims 28 and 32-33), as suggested by the Examiner. Support for purified antibodies is found e.g. on page 20, line 16-18 of the published PCT application.

Rejection under 35 U.S.C. 112, first paragraph (items 8 and 9)

The KRIX-1 cell line has been deposited by one of the inventors (Dr. M. Jacquemin) in a recognized depository institution resorting under the Budapest Treaty as mentioned in the specification of the published PCT application on page 12, from line 6 onwards: "*The cell line named KRIX 1 producing monoclonal antibodies was deposited with the BCCM™/LMBP (Belgian Coordinated Collections of Microorganisms) plasmid collection laboratorium voor moleculaire biologie, University of Ghent K.L. Ledeganckstraat 35, B-9000 Ghent, BE under accession number LMBP 5089CB on July 1, 1999.*"

The deposit is thus present in a public depository and in accordance with rule 9.1 of the Budapest Treaty. A copy of the receipt provided to Applicant by the BCCM indicating that this deposit was

received under the Budapest Treaty, as well as the requested statement with regard to its availability are attached.

Given this statement and Applicant's Declaration (signed document to be filed when available), Applicant maintains that the requirements of section 112 have been satisfied. The section 112 rejection should therefore be withdrawn.

Rejection under 35 U.S.C. 112, first paragraph (items 10 and 11 of the *Office Action*)

The Examiner has indicated that the written description is not commensurate with the scope of the claims and in that the specification is not enabling for antibodies other than those described. Without acquiescence to the Examiner's objection, Applicant hereby submits a new set of claims in which the scope has been limited to the antibodies KRIX-1 and antibodies and fragments directly derived therefrom. It is respectfully submitted that the specification provides a full characterization of the KRIX-1 antibody including the sequence of its variable domains. Moreover the specification provides a test method for assaying FVIII inhibitory activity. The present invention demonstrates the usefulness of antibodies which do not completely inhibit FVIII activity and provides the full characterization of one such antibody. Thus, the skilled person could, with a limited effort and based on standard methods in the art, produce minor variants of this antibody having a similar usefulness. For instance, using the information in the specification on epitope-mapping and assaying FVIII activity, a large set of antibodies derived from Krix-1 by random mutations in the variable chains can be screened in parallel for binding to the C1 domain. Positive antibodies can than further be screened for there inhibiting properties. Thus it is submitted not only that there is adequate written description for the scope of the claims presently submitted, but that a further limitation of the claims would not be commensurate with the contribution of the invention to the art and would make it easy for competitors to use the invention while working outside of the scope of the claims.

In this regard, Applicant submits that modifications of Krix-1, were envisaged within the scope of the invention in the application as filed which specifies:

On page 12, line 18-20: *"Where the ligands in accordance with the present invention include amino acid sequences, homology may include having at least 80%, more preferably 90% and most preferably 95% amino acid sequence identity with the relevant ligand."*

And

On page 16 line 6-12: *"More preferably the said monoclonal antibody is a human monoclonal antibody or fragment or derivative or homolog thereof obtainable from cell line krix 1 deposited with the belgian co-ordinated collections of micro-organisms under accession number lmbp 5089cb. The degree of homology is preferably at least 80%, more preferably 90 %, and most preferably 95%*

and the homology is preferably particularly referenced in respect to the complementarity determining regions. A ligand in accordance with the present invention may also include a synthetic polypeptide of equivalent potency."

In order to avoid any lack of clarity with regard to the scope of the claims, the term "homolog" has been omitted from the claims.

Applicant furthermore *disputes* contravenes the argument of the examiner against the claims to the pharmaceutical compositions in that the data are not sufficiently predictive for the in vivo use of the antibodies (page 5, last paragraph of the *Office Action*).

It is respectfully submitted that the pharmaceutical usefulness of the present invention is supported by the in vivo data presented in Example 7 on page 28 of the specification. The present invention solves a major problem in the prior art, which is the provision of an anticoagulant which can be administered without the risk of overdosing and rendering a patient at risk of severe bleedings. The compounds of the present invention ensure inhibition of Factor VIII to a limited level, so that some FVIII activity remains to perform vital functions, as illustrated by Example 7. Using a physiological excess (1600 microgram/kg) of Krix-1 a partial reduction of FVIII activity (from 1.6 to 0.3 IU/ml) is obtained (page 28, lines 36-39 of the published PCT application). This example further shows that a reduction in thrombus size is achieved when Krix-1 antibody is used (page 28, line 28-30).

Thus, it is respectfully submitted that the specification does demonstrate that the compositions of the invention can be beneficial as a pharmaceutical composition.

With regard to the objection of the Examiner to the smaller antibody fragments (page 6, first paragraph of the *(Office Action)*, it is respectfully submitted that this objection has been rendered partially moot in that the claims no longer refer to individual CDRs. Applicant respectfully submits that the other fragments listed in the claims presently filed (more particularly claims 50 and 53), i.e. Fab, F(ab)2 and scFv fragments should not be objected to by the Examiner, as these are routinely produced in the art and often found to retain at least part of the inhibitory activity of the antibody they are derived from. Thus it is respectfully submitted that the skilled person would have no difficulties in obtaining based on methods described in the art and the application as filed, antigen-binding Fab, F(ab)2 or scFv fragments from the Krix-1 antibody disclosed in the application as filed.

Rejection Objection under 35 U.S.C. 102 (items 12-14 of the *Office Action*)

a) anticipation by Lenting et al. (1994, J. Biol. Chem. 269, 7150-7165)(item 13)

The claims presently submitted have been amended to refer only to the LE2E9 (" Krix-1") antibody and fragments or to antibodies with similar sequences in the heavy and light chains. The Krix-1 antibody was developed by the inventors and was not previously available to other researchers.

The article cited by the Examiner describes an antibody which binds to a region of FVIII "comprising" the C1 domain. At the time, the exact binding site on FVIII was not known to the authors. However, a later published article of the same authors [Lenting et al. J Biol Chem. (1996) 271, 1935-1940 – copy enclosed] mentions in the abstract: "Previous studies have shown that the interaction between factor IXa and VIII involves the light chain of factor VIII and that this interaction inhibited by the monoclonal antibody CLB-CAg A against the factor VIII region Gln1778-Asp1840 (Lenting, P.J., Donath, M.J.S.H., van Mourik, J.A., and Mertens, K. (1994) J. Biol. Chem. 269, 7150-7155). Employing distinct recombinant factor VIII fragments, we **now have localized the epitope of this antibody more precisely between the A3 domain residues Glu1801 and Met1823.**" (emphasis added).

Thus, it is respectfully submitted that this later publication makes it clear that the Lenting et al. 1994 article describes an antibody that binds to the A3 domain of FVIII, and thus that this publication does not anticipate the C1 binding antibodies of the present invention.

b) Anticipation by Jacquemin et al. (1998, Blood 92, 496-502)(item 14).

The inventors of the present application are Marc Jacquemin and Jean-Marie Saint Remy. The present application claims a priority of July 14, 1999 of US application 60/143,891.

The cited article features both inventors and was published on July 15, 1998, which is less than one year before the filing of the priority application of the present application.

It is respectfully submitted that this reference by the inventors and, being published in the grace period, should not be considered as prior art for the present application.

Rejections under 35 U.S.C. 103(a) (item 15-20 of the Office Action)

It is herewith confirmed that the subject matter of the various claims was commonly owned at the time any inventions covered thereby were made.

Moreover, it is submitted that, without acquiescence to the rejections of the claims previously on file, the limitation of the claims as filed herewith should render the obviousness objections moot. Indeed, the claims filed herewith relate to antibodies or antigen-binding fragments thereof, which are all derived from the monoclonal antibody Krix-1. However, in order to further the acceptance of the application and, in view of the fact that it is believed that these objections are not justified even with respect to the broader scope of the invention, i.e. the provision of inhibitory antibodies against the C1 domain of FVIII, the objections of the Examiner are addressed hereafter.

a) Obviousness over Peerlinck et al. in view of US 6,602,015 (item 16)

The cited article of Peerlinck K, **Jacquemin MG**, Arnout J, Hoylaerts MF, Gilles JG, Lavend'homme R, Johnson KM, Freson K, Scandella D, **Saint-Remy JM**, Vermylen J. Blood 93 2267-2273 was published in April 1999. This article also refers to research performed by the inventors (names indicated in bold).

It is respectfully submitted that also this reference document, being published in the grace period should not be taken in account for the examination of the present invention.

The '015 patent teaches how peripheral blood lymphocytes of animals can be used for the production of monoclonal antibodies. It does not mention FVIII, or any coagulation factors for that matter. Moreover the '015 patent relates to autoantibodies which enhance the rate of a chemical reaction. This is contrary to the present invention which relate to inhibitory antibodies. It is respectfully submitted that this reference alone does not suggest in any way that antibodies against the C1 domain of FVIII can be made. *A fortiori* this reference in no way suggests the subject of the claims presently submitted, i.e. antibodies from the Krix-1 cell-line and fragments or derivatives thereof.

b) Obviousness over Gilles et al. in view of US 6,602,015 (item 16)

The IDS statement of the USPTO mentions for the Gilles et al. abstract a publication date of November 15, 1998. The authors of the abstract include M. Jacquemin and J.-M Saint-Remy, the inventors named on the present application. Thus, this reference was also published within the grace

period before the filing date of the priority of the present application and should not be taken in account for the examination of the present invention.

As detailed above, it is respectfully submitted that the '015 patent alone can not be considered to disclose or suggest the subject matter of the present invention.

c) Obviousness over Peerlinck et al. or Gilles et al. in view of US 6,602,015 and Owens et al (1994) (item 17).

As mentioned above the Peerlinck et al. and Gilles et al. *references* were published within the grace period before the priority filing of the present application and can not be cited under 35 U.S.C. 103(a).

Owens et al. (1994) is a general review on the development of antibody fragments and humanized antibodies for therapeutic treatment. It does not describe or suggestion the production of antibodies against FVIII, or any other coagulation factors. It is respectfully submitted that Owens et al. neither alone, nor in combination with the '015 patent cited by the Examiner, suggests the monoclonal inhibitory antibodies which are directed against the C1 domain of FVIII as disclosed by the present invention.

d) Anticipation by Jacquemin et al. or US 5,744,446 in view of Campbell (item 19).

As detailed above, the Jacquemin et al. citation was published within the grace period before the priority of the present application.

The Examiner states that the '446 patent teaches that inhibitory antibodies specific for the C1 domain can be isolated. It should be noted however that while the '446 describes a general procedure for epitope mapping and characterization of anti-FVIII antibodies, it also indicates that auto-antibodies against the C1 domain are unlikely to exist as this domain is not believed to be of clinical importance (column 19, line 15-20): "*It is likely that clinically significant factor VIII epitopes are confined to the A2 and C2 domains. However, if antibodies to other regions (A1, A3, B or C1 domain) are identified, the epitopes can be mapped and eliminated by using the approach described herein* ..."(emphasis added). Similarly, in column 17, lines 13-19 of the '446 patent, the relevance of the C1 epitope (and thus the existence of antibodies thereto) is questioned "*In addition to the A2 and C2 epitopes, there may be a third epitope in the A3 or C1 domain of the light chain of factor VIII, according to Scandella et al., 82 Blood 1767-1775 (1993). The significance of this putative third epitope is unknown, but it appears to account for a minor fraction of the epitope reactivity in factor*

VIII." (emphasis added). Thus the '446 indicates that, if at all present, anti-C1 antibodies are present in minor quantities. It is submitted that the skilled person would not be motivated to isolate or develop inhibitory antibodies directed against the C1 domain based on this disclosure. A fortiori, this disclosure in no way suggests the purified Krix-1 inhibitory antibodies or antibodies derived therefrom.

Summarizing, it is submitted that at the time of filing, the skilled person was of the opinion that for inhibition of FVIII, the C1 domain was not an important epitope. Thus, there was no motivation to identify or develop such antibodies.

e) rejections under 35 U.S.C. 103(a) to former claims 38-43 (items 17-18)

It is furthermore submitted that none of the references which can be cited against the present application disclose the methods of the invention (as suggested in items 16-18 of the Office Action). The cited '015 method describes how lymphocytes of animals can be used for the production of monoclonal antibodies. It does not relate to the production of inhibitory FVIII antibodies and does not disclose or suggest that these lymphocytes should be taken from animals having a FVIII deficiency due to a modification in the C1 domain. Nor does the '015 patent suggest immunization with wild-type FVIII. Thus, the methods of the invention, a fortiori as claimed in the claims filed herewith, i.e. limited to the C1 domain of FVIII, are inventive over the prior art.

f) rejection under 35 U.S.C.103(a) to claims 35-36 (item 20)

It is respectfully submitted that the rejections under 35 U.S.C. 103 against the claims covering pharmaceutical compositions (former claims 35-36 and present claims 53-55) are justified to an even lesser extent. The cited references have been discussed hereinabove, and it is not necessary to repeat the arguments that these references do not suggest or disclose the antibodies of the invention per se. It is however respectfully submitted that the present invention not only provides the teaching that inhibitory antibodies to the C1 domain can be obtained, but moreover that they have the advantage of only partially inhibiting FVIII when administered in physiological excess. This is of vital importance in their pharmaceutical application, as they allow these antibodies to be administered to a patient in need of an anticoagulant without the risk of severe bleeding. There is no mention of a partial inhibition of FVIII, or the therapeutic advantage thereof in any of the cited documents. Indeed, the Examiner fails to recite any such reference about the particular usefulness of anti-C1 antibodies in the Office

Action. It is thus submitted that the claims to the pharmaceutical compositions comprising the antibodies of the invention should *a fortiori* be considered allowable over the prior art.

Given the above, it is submitted that this application is in condition for allowance, and such action is solicited.

Respectfully submitted,

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